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Myasthenia Gravis in the Elderly: Differential Diagnosis and Management

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Abstract Late-life disorders presenting with weakness often have a delay in diagnosis leading to decreased quality of life and impairment of mobility. Myasthenia gravis is an immune disorder affecting the neuromuscular junction resulting in varying levels of weakness in the orbital, bulbar, and limb muscles. The evaluation of weakness in the elderly should be geared toward treatable and reversible causes such as myasthenia gravis. The major treatment options include symptomatic, immunosuppressive, and immunomodulating therapies.

Keywords Myasthenia gravis · Neuromuscular junction · Immunotherapy · Monoclonal antibody · Fatigue · Acetylcholine receptor antibody · MUSK antibody · Intravenous immunoglobulin · Elderly · Thymoma · Thymectomy · Ptosis · Dysphagial · Dysarthria

Introduction

Myasthenia gravis (MG) is an immune disorder of the neuromuscular junction (NMJ). MG has an incidence of 1–2 per 100,000 making it a rare disease [1], and more than 50 % of cases are diagnosed in patients older than 65 [2•]. This makes awareness of MG important as it is a treatable disease if diagnosed in a timely manner. The incidence of MG in elderly patients has been rising due to multiple factors including an aging population, increased detection, and increased awareness [3]. There have been recent studies looking at the genetic and environmental basis of MG. It has been found that monozygotic twin concordance is approximately 35 % [4]. This provides strong evidence for environmental factors that make patients susceptible along with other factors such as gender and sex hormones. Future research in the area of T cell differentiation and signaling pathways will likely shed light on the genetic basis of MG and possibly affect the treatment approach.

Patients presenting with weakness and fatigue should be evaluated in an orderly manner. This starts with a complete history and neurological examination. Patients with MG often are not aware of their neurologic deficits. A careful neuromuscular examination will often show signs of fatigable weakness that is the hallmark of MG. There are two main ways that MG can present with symptoms. Patients with ocular MG have symptoms that only involve the eyes, such as ptosis and diplopia. Patients with generalized MG can have symptoms that involve any combination of ptosis, diplopia, dysphagia, respiratory involvement, and generalized weakness that is usually most prominent in proximal limb muscles. Patients who initially present with ocular MG can go on to develop generalized MG. One retrospective study of 158 patients with ocular MG showed that 20 % of patients converted to generalized MG with or without immunosuppressive therapy with one third of those patients converting after 2 years and no significant risk factors identified [5].

Once MG is in the differential diagnosis, the evaluation should follow in an orderly fashion. Electrodiagnostic testing with repetitive nerve stimulation is an important first step to assess for a disorder of neuromuscular transmission. The

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routine electrodiagnostic studies of nerve conduction and needle electromyography (EMG) of motor unit action potentials (MUAPs) are typically normal. If the diagnosis of MG is still strongly suspected, but the repetitive nerve stimulation testing is normal, then single-fiber EMG can be helpful. The findings on single-fiber EMG that can diagnose a NMJ disorder are known as jitter and blocking. The NMJ has a normal small amount of instability associated with it, which is known as jitter and is seen on single-fiber EMG when the same motor unit cannot be completely superimposed. When the amount of jitter is increased, this is abnormal and indicates a problem in NMJ transmission. Blocking is seen when the motor unit is sometimes not present or blocked due to severe dysfunction of NMJ transmission. A prospective single-blind study of single-fiber EMG of the orbicularis oculi muscle in 100 patients showed a very high negative predictive value of 97 % and a positive predictive value of 79 % [6•]. Blood work for acetylcholine receptor (AChR) binding, blocking, and modulating antibodies as well as muscle-specific receptor tyrosine kinase (MUSK) antibodies should be ordered as a next step. The percentage of patients positive for AChR antibodies does not differ significantly between younger and elderly patients, but the antibody titers tend to be lower in elderly patients [7]. AChR antibody levels do not correlate well with clinical severity as levels fall in patients who clinically improve but also in many patients who do not improve [8]. Recently, there has been more interest in patients with double-seronegative MG, those patients who do not have AChR or MUSK antibodies but have the typical symptoms and electrodiagnostic findings of MG. Multiple groups have found varying percentages of these patients to have lipoprotein-related protein 4 (LRP4) antibodies [9, 10]. LRP4 antibodies have also been found in elderly patients with isolated ocular MG [11]. Imaging of the anterior mediastinum with CT or MRI is important to evaluate for a thymoma, which is more common in the elderly population [2•].

Once the diagnosis of MG is made, an organized approach to treatment is critical. The first decision is whether the patient is stable enough to be treated as an outpatient or needs inpatient treatment. The next decision is the best choice of immunotherapy to stabilize the patient and eventually bring a long-term remission.

Differential Diagnosis

Elderly patients with MG typically present with similar symptoms to younger patients with general limb weakness or ocular symptoms and less often with bulbar symptoms [7]. The differential diagnosis is much wider in elderly patients compared to younger patients. MG can be misdiagnosed as many different diseases, including cerebral infarctions, especially brainstem infarctions, heart failure, amyotrophic lateral sclerosis, cachexia, and Guillain-Barre syndrome as well as myopathic disorders. An 84-year-old man with dysarthria, dysphagia, and a choking cough was initially diagnosed with a cerebral infarction but later diagnosed with MG when his symptoms returned and he was found to have ptosis that worsened later in the day [12]. As findings such as blocking on EMG can cause MUAPs to appear to be smaller and of shorter duration, a NMJ disorder such as MG can mimic a myopathic disorder. Four patients of varying ages with proximal weakness who underwent a muscle biopsy for suspected myopathy were later found to have MG or a congenital myasthenic syndrome [13]. It is important to consider the diagnosis of MG in any patient with diplopia, ptosis, and facial weakness and perform the appropriate testing.

Treatment (Table 1)

Pyridostigmine

Pyridostigmine is an acetylcholinesterase inhibitor that is used for symptomatic treatment but does not affect the underlying disease process. In some cases of ocular myasthenia, pyridostigmine alone may be sufficient to control symptoms with no immunosuppression needed. However, in the majority of MG cases, this medication is not sufficient alone but can still be helpful to control symptoms, especially early in the course. Pyridostigmine is typically dosed at 60–120 mg every 3 to 8 h in the regular release form. There is a slow-release form available, but the absorption is unreliable and this formulation is not commonly used. Pyridostigmine can have many side effects that are due to the cholinergic effects and can include diarrhea and increased secretions. Pyridostigmine should be held if a patient is intubated due to the increased secretions. The side effects may be more severe in elderly patients, and some have advocated that pyridostigmine should not be the first-line treatment in this group [2•].

Corticosteroids

Oral corticosteroids are the first line of immunosuppressive treatment and the most commonly used treatment in MG. Oral prednisone is the most commonly used steroid. Prednisone is typically started at doses of 0.75 to 1 mg/kg/day, usually at a total dose of 60–80 mg daily. However, some clinicians advocate starting at lower doses and increasing the dose over days to weeks to prevent the temporary worsening of symptoms that occur when starting high-dose prednisone, especially in patients that present with more severe symptoms. The high dose of prednisone is maintained until the patient improves and is then slowly tapered over months. Most

Table 1 Treatments used in myasthenia gravis

Medication	Use	Dosing	Side effects
Pyridostigmine	Symptomatic treatment	60–120 mg every 3–8 h	Diarrhea Increased secretions
Prednisone	First-line immunosuppression	1 mg/kg/day then taper over months	Weight gain Hypertension Diabetes Osteoporosis Glaucoma
IVIG	Acute exacerbation Maintenance dosing, especially when waiting for steroid-sparing agents to have effect	Acute or loading dose 2 g/kg divided over 4–5 days Maintenance dosing 1 g/kg/month divided every 2–4 weeks	IgA allergic reaction Infusion reactions Thromboembolic events
PLEX	Acute exacerbation	One exchange every other day for at least three to five exchanges	Catheter insertion Hypocalcemia Hypotension
Azathioprine	First-line steroid-sparing agent	Start 50 mg daily, then increase to 100–150 mg daily	Liver dysfunction Bone marrow suppression
Mycophenolate mofetil	Second-line steroid-sparing agent	500–1000 mg BID	Infection Lymphopenia Lymphoproliferative disorders Progressive multifocal leukoencephalopathy
Methotrexate	Second-line steroid-sparing agent	7.5–25 mg weekly with folate supplementation	Hepatotoxicity Renal failure Bone marrow suppression Peptic ulcers Neurotoxicity
Cyclosporin A	Second-line steroid-sparing agent	Start at 2.5 mg/kg/day in divided doses and can increase up to 4 mg/kg/day	Nephrotoxicity Hyperglycemia Hypertension
Tacrolimus	Second-line steroid-sparing agent	1–5 mg daily	Nephrotoxicity Hyperglycemia Hypertension
Cyclophosphamide	Refractory disease	Variable	Bone marrow suppression Cardiotoxicity Nausea and vomiting Hepatotoxicity Hemorrhagic cystitis
Rituximab	Second-line steroid-sparing agent	375 mg/m^2 weekly for 4 weeks with repeat dosing every 6 months	Infusion reactions Hepatitis B reactivation Renal toxicity Progressive multifocal leukoencephalopathy
Eculizumab	Second-line steroid-sparing agent	Variable	Infusion reaction Infections, especially meningococcal meningitis
Thymectomy	In any patient with a thymoma, consider in younger patients without thymoma	Open versus minimally invasive techniques	Surgical related

patients cannot tolerate the tapering of the steroids without a worsening of symptoms. Some neurologists use every-other-day dosing of steroids as this is thought to cause less side effects, although this has never been shown in a randomized double-blind trial. As steroids have significant adverse effects when used on a long-term basis, such as weight gain, hypertension, diabetes, osteoporosis, and glaucoma, the recommendation is to decrease the steroid dose as much as possible or try to stop the steroids with the use of other immunosuppressive or steroid-sparing agents. Oral prednisone dosing tends to be

lower in elderly patients compared to younger patients with similar rates of side effects related to steroid use [2•, 7]. A recent study comparing MG patients on oral prednisone with patients not on oral prednisone showed that patients who had minimal symptoms or better at the highest dose of prednisone and also treated with intravenous immunoglobulin (IVIG) or plasmapheresis (PLEX) were more likely to have minimal symptoms or better of MG later in the course of the disease. Also, patients who were on the highest total dose of prednisone in the last year were less likely to have well-controlled MG symptoms [14•].

IVIG and PLEX

The typical treatment for a myasthenic crisis is either intravenous IVIG or PLEX. The IVIG is usually given at a dose of 2 g per kilogram over 2 to 5 days. PLEX is typically performed every other day for a total of five or more treatments and has been shown to be safe and effective [15]. A randomized and blinded study comparing IVIG and PLEX in the treatment of moderate to severe MG with worsening weakness showed no difference between the treatments with similar proportions of patients responding to the treatment in both groups [16]. Fewer elderly patients required IVIG and PLEX in one study, but the treatments were more effective [7]. IVIG can be used on a recurring basis in the treatment of MG with doses of 1 g/kg per month used in dosing varying from 1 day every other week to two consecutive days every month. This is often used in combination with oral agents when the oral agents are not providing enough symptom relief, when oral agents have been started but are not yet effective, or when there are multiple episodes of myasthenic crisis. Complications of PLEX include complications related to placement of the catheter, hypocalcemia, paresthesia, muscle cramps, nausea, and vomiting. Prior to the use of IVIG, the level of immunoglobulin A (IgA) should be checked as alternate formulations need to be given if the IgA level is low to prevent a severe allergic reaction. Side effects of IVIG are usually directly related to the speed of infusion and include rash, fever, and headache. More serious, although rare, side effects of IVIG are thromboembolic events that cause cerebral infarction or myocardial infarction and renal failure.

Azathioprine

Azathioprine is a nonspecific immunosuppressive that inhibits DNA replication and purine synthesis. It is the recommended first-line steroid-sparing agent. Azathioprine is typically started at 50 mg daily and increased to 100–150 mg daily over 2–3 months. At the higher doses, azathioprine may have to be split into two or three doses due to dyspepsia. Azathioprine is often started at the same time as corticosteroids, as the full immunosuppressive effect can take 3–9 months. Thiopurine methyltransferase (TPMT) is an enzyme that inactivates one of the metabolites of azathioprine. The FDA recommends, but does not require, that the TPMT enzyme is measured prior to starting azathioprine and a reduced dose or alternate medication should be considered if the level of the enzyme is low. Azathioprine has many side effects that include liver dysfunction, bone marrow suppression, and increased risk of cancer. Bone marrow suppression and liver dysfunction can be monitored with blood work. Blood work including hepatic enzymes and a complete blood count should be performed monthly for the first 3–6 months of use and followed regularly every 3–6 months. Azathioprine can have important interactions with other medications. Azathioprine is contraindicated to be used with allopurinol and can increase the metabolism of warfarin. Azathioprine use with angiotensin-converting enzyme (ACE) inhibitors can enhance bone marrow suppression [2•].

Mycophenolate Mofetil

Mycophenolate mofetil selectively inhibits the proliferation of B and T lymphocytes. There have been questions about the efficacy in MG, as two randomized controlled trials of mycophenolate in conjunction with prednisone demonstrated no benefit over prednisone alone at 3 months or a steroid-sparing effect at 9 months [17, 18]. A retrospective, multicenter study showed treatment efficacy after 12 months when used as a monotherapy or with prednisone [19]. There have been criticisms that the randomized controlled trials were too short to show benefit. A recent retrospective study showed that mycophenolate mofetil could be safely tapered in 67 % of patients without relapse with more success with a slower taper [20•]. Many clinicians continue to use mycophenolate mofetil for the treatment of MG as a steroid-sparing agent, although azathioprine is still recommended as the first-line agent. Most patients are maintained on a dose of 1000–1250 mg twice daily. The side effects of mycophenolate mofetil include infections, lymphopenia, lymphoproliferative disorders, and progressive multifocal leukoencephalopathy.

Methotrexate

Methotrexate is a structural analog of folic acid that interferes with DNA synthesis. It is considered the disease-modifying agent of choice in rheumatoid arthritis. Typically dosed on a weekly basis, methotrexate is a less expensive medication compared to azathioprine or mycophenolate. A randomized single-blind study that compared methotrexate 17.5 mg weekly to azathioprine at 2.5–3 mg/kg daily in patients recently diagnosed with generalized MG showed no significant difference in daily prednisone dose at 2 years, and both medications allowed the steroid dose to be reduced [21]. There was a double-blind placebo-controlled trial of methotrexate versus

placebo in patients on prednisone treatment that was recently completed that showed no difference in prednisone dosing between the methotrexate and placebo groups [22, 23••]. Side effects include hepatotoxicity, renal failure, bone marrow suppression, peptic ulcers, and neurotoxicity.

Cyclosporin A

Cyclosporin A inhibits T cell activation and inhibits antigen-specific proliferation of T lymphocytes. The side effects of cyclosporine A include nephrotoxicity, hyperglycemia, and hypertension. Cyclosporin A was used in three elderly women with MG ranging from 81 to 83 years of age with side effects from steroid treatment that resulted in improvement in symptoms and reduced steroid dosing. The cyclosporin A had to be discontinued in one patient due to elevated creatinine that improved with stopping it [24•]. Cyclosporin A is recommended as a second-line agent, especially in elderly patients due to the nephrotoxicity.

Tacrolimus

Tacrolimus also inhibits T cell activation and inhibits antigen-specific proliferation of T lymphocytes. It can be used as a steroid-sparing medication but is not currently used frequently in the treatment of MG. A recent randomized, double-blind, placebo-controlled study of patients with MG well controlled on oral steroids of tacrolimus at 3 mg daily showed no steroid-sparing effect in the primary analysis, although there was some suggestion of steroid-sparing effects in the secondary analysis [25]. More studies are needed to show if tacrolimus can be included with the other steroid-sparing medications typically used in MG.

Cyclophosphamide

Cyclophosphamide is a potent immunosuppressant that decreases DNA synthesis. It is only used in patients who have failed multiple other agents due to its high toxicity. Side effects include bone marrow suppression, cardiotoxicity, nausea and vomiting, hepatotoxicity, and hemorrhagic cystitis.

Rituximab

Rituximab is an anti-CD20 antibody that targets B lymphocytes. This medication is considered in patients with refractory MG who have failed several other treatments. Rituximab is not currently approved for the treatment of MG and can only be prescribed "off-label." Rituximab dosing regimens can vary from 375 mg/m^2 weekly for 4 weeks with repeat dosing every 6 months to 1 g every 2 weeks for two doses with 1 g as needed if symptoms worsen. A retrospective study of 20 patients, 13 with refractory MG, showed fewer relapse rates and lower steroid doses in refractory patients and no steroids in nonrefractory patients 18 months after starting rituximab [26]. There is currently an on-going randomized double-blind placebo-controlled trial of rituximab dosed at 375 mg/m^2 weekly for 4 weeks in two cycles 6 months apart with a primary endpoint of the number of subjects who can reduce prednisone dosing by more than 75 % and is due to be completed in 2017 [27••]. Side effects of rituximab include infusion reactions, hepatitis B reactivation, renal toxicity, and progressive multifocal leukoencephalopathy.

Eculizumab

Eculizumab is a monoclonal antibody that blocks activation of complement. It is currently only approved for use in paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome. A phase II multicenter double-blind placebo-controlled crossover study of eculizumab in 14 patients with severe, refractory generalized MG who were also on other immunosuppressive medications showed a significantly reduced disease severity score with no increase in adverse events [28]. Side effects include infusion reactions and infections, especially meningococcal meningitis.

Thymectomy

Thymomas are common in patients with MG and should be screened for in every patient with a CT or MRI of the chest as they can occur in 10–15 % of patients [1]. Thymectomy, removal of the thymoma, is the standard treatment if a thymoma is found. Younger patients with MG are more likely to undergo thymectomy, but thymectomy should be strongly considered in any age of patient with a thymoma. Thymectomy can improve the symptoms of MG and decrease the need for medications over the long-term and has been associated with remission in certain cases. There is even some evidence that thymectomy in patients without thymoma can be beneficial. There are multiple approaches that can be used for a thymectomy, but removal of all thymoma tissue is associated with higher rates of remission with an open thymectomy being traditionally recommended for this reason. A recent study that evaluated minimally invasive thymectomy (MIT) versus open thymectomy in MG patients demonstrated shorter lengths of stay with the MIT group with similar rates of remission in a small subgroup that was available for analysis [29]. The role of extended thymectomy via median sternotomy in patients with ocular or very mild MG was studied retrospectively and compared to patients who were managed medically. The thymectomy patients achieved a more rapid remission although the overall remission rates were similar between the groups and there were significantly better outcomes if the thymectomy was performed within 6 months of the onset of symptoms [30]. Another study compared video-assisted thymectomy to

transsternal thymectomy in patients with generalized MG and found no difference in remission rates or length of hospital stay, but the video-assisted group spent a shorter time in the intensive care unit [31].

Surgery is a known cause of myasthenic crisis in MG. There is some evidence that IVIG or PLEX done prior to surgery may decrease the rate of myasthenic crisis after surgery. A randomized double-blind placebo-controlled trial of IVIG prior to surgical procedures requiring anesthesia is ongoing in Spain [32•].

Adjunct Treatments

Patients who are on chronic steroid treatment should be on concurrent vitamin D and calcium supplementation to prevent the development of osteopenia and osteoporosis. Older patients, especially those already with osteopenia or osteoporosis, should be on a bisphosphonate. A recent study published in 2012 showed that vitamin D levels were lower in patients with MG compared to healthy controls and there was improvement in fatigue scores in some patients after supplementation [33]. Vitamin D monitoring and supplementation may provide benefit in some patients with MG.

Outcome with Treatment

The symptoms of MG are often most significant in the first few years with clinical improvement following. There is a lot of variability in levels of exacerbations, improvement, remission, or delayed recurrence. The factors associated with worsening symptoms and exacerbations were studied in 100 patients with MG with more exacerbations seen in patients older than 60. There were more episodes of worsening symptoms in the first year although the rates of exacerbations and worsening symptoms after the first year remained steady in spite of the length of disease. Only 6 % of the patients achieved clinical remission off of medication with only one patient achieving remission with generalized MG, and 39 % achieved clinical remission while on medication [34•]. Clinical remission is possible and should be the goal even if the patient requires prolonged immunosuppression.

Conclusion

MG is a rare but serious condition that affects all age groups but is being diagnosed more often in the elderly. Consideration of the diagnosis of MG in any patient with diplopia, ptosis, and facial weakness is important, and confirmatory testing should be performed as the differential diagnosis is more extensive in elderly patients. Treatment of MG includes symptomatic treatment with pyridostigmine and immunosuppression. Corticosteroids are the first-line immunosuppressant, although steroid-sparing agents are often needed due to the high occurrence of side effects. Azathioprine is the recommended first-line steroid-sparing agent, but other agents can be considered based on efficacy and side effect profile. Thymectomy should be considered in any patient that has a thymoma, including elderly patients. There are several studies that show that MIT may be just as effective as open thymectomy with fewer days spent in the ICU, which may be an important consideration in elderly patients. Clinical remission is possible in MG, although most patients do require some level of continuous immunosuppression to achieve this.

Compliance with Ethical Standards

Conflict of Interest Jonathan Goldstein and Erin Manning declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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